



Lenalidomide with or without erythropoietin in transfusion-dependent erythropoiesis-stimulating agent-refractory lower-risk MDS without 5q deletion

Andrea Toma, O. Kosmider, S. Chevret, J. Delaunay, A. Stamatoullas, C. Rose, O. Beyne-Rauzy, A. Banos, A. Guerci-Bresler, S. Wickenhauser, et al.

► To cite this version:

Andrea Toma, O. Kosmider, S. Chevret, J. Delaunay, A. Stamatoullas, et al.. Lenalidomide with or without erythropoietin in transfusion-dependent erythropoiesis-stimulating agent-refractory lower-risk MDS without 5q deletion. *Leukemia*, 2016, 30 (4), pp.897–905. 10.1038/leu.2015.296 . hal-01321412

HAL Id: hal-01321412

<https://hal-univ-rennes1.archives-ouvertes.fr/hal-01321412>

Submitted on 6 Oct 2016

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Copyright

Lenalidomide with or without Erythropoietin in transfusion dependent erythropoiesis-stimulating agent-refractory lower risk MDS without 5q deletion

Running title: Lenalidomide in transfused non del 5q low risk MDS

Andrea Toma¹, Olivier Kosmider², Sylvie Chevret³, Jacques Delaunay⁴, Aspasia Stamatoullas⁵, Christian Rose⁶, Odile Beyne-Rauzy⁷, Anna Banos⁸, Agnes Guerci-Bresler⁹, Stefan Wickenhauser¹⁰, Denis Caillot¹¹, Kamel Laribi¹², Benoit De Renzis¹³, Dominique Bordessoule¹⁴, Claude Gardin¹⁵, Bohrane Slama¹⁶, Laurence Sanhes¹⁷, Berangere Gruson¹⁸, Pascal Cony Makhoul¹⁹, Bachra Chouffi²⁰, Celia Salanoubat²¹, Riad Benramdane²², Laurence Legros²³, Eric Wattel²⁴, Gerard Tertian²⁵, Kamal Bouabdallah²⁶, François Guilhot²⁷, Anne Laure Taksin²⁸, Stephane Cheze²⁹, Karim Maloum³⁰, Stanislas Nimuboma³¹, Carole Soussain³², Françoise Isnard³³, Emmanuel Gyan³⁴, Raphael Petit³⁵, Julie Lejeune³, Veronique Sardnal², Aline Renneville³⁶, Claude Preudhomme³⁶, Michaela Fontenay², Pierre Fenaux^{37*}, François Dreyfus^{38*}

* equally contributed as last authors

¹Hematology Department, Hopital Universitaire Henri Mondor, Assistance Publique-Hôpitaux de Paris (APHP) and Paris 12 University, Creteil, France

²Assistance Publique-Hopitaux de Paris, Hopital Cochin, Laboratory of Hematology & Paris Descartes University, Paris, France

³Biostatistics Team (ECSTRA), UMR1153, Inserm, Hopital Saint Louis, APHP and Paris 7 University, Paris, France

⁴Hematology Departement, Centre Hospitalier Universitaire, Nantes, France

⁵Hematology Departement, Centre Henri Becquerel, Rouen, France

⁶Hematology Departement, Hopital Saint Vincent de Paul, Lomme, France

⁷Hematology Departement, Centre Hospitalier Universitaire, Purpan, France

- ⁸Hematology Departement, Centre Hospitalier Universitaire, Strasbourg, France
- ⁹ Hematology Departement, Centre Hospitalier Universitaire, Nancy, France,
- ¹⁰Hematology Departement, Centre Hospitalier Universitaire, Nimes, France
- ¹¹Hematology Departement, Centre Hospitalier Universitaire, Dijon, France
- ¹² Hematology Departement, Centre Hospitalier, Le Mans, France
- ¹³ Hematology Departement, Centre Hospitalier Universitaire, Clermont Ferrand, France
- ¹⁴Hematology Departement, Centre Hospitalier Universitaire, Limoges, France
- ¹⁵Hematology Departement, Hopital Avicenne, APHP, and Paris 13 University Bobigny, France
- ¹⁶ Hematology Departement, Centre Hospitalier, Avignon, France
- ¹⁷ Hematology Departement, Centre Hospitalier, Perpignan, France
- ¹⁸ Hematology Departement, Hopital Universitaire Amiens, France
- ¹⁹ Hematology Departement, Centre Hospitalier, Annecy, France
- ²⁰ Hematology Departement, Centre Hospitalier, Boulogne sur Mer, France
- ²¹ Hematology Departement, Centre Hospitalier, Corbeil, France
- ²² Hematology Departement, Centre Hospitalier, Pontoise, France
- ²³ Hematology Departement, Centre Hospitalier Universitaire, Nice, France
- ²⁴ Hematology Departement, Centre Hospitalier Edouard Herriot, Lyon, France
- ²⁵ Hematology Departement, Hopital Kremlin Bicetre, APHP, Kremlin Bicetre, France
- ²⁶ Hematology Departement, Centre Hospitalier Universitaire, Bordeaux, France
- ²⁷ Hematology Departement, Centre Hospitalier Jean Bernard, Poitiers, France
- ²⁸ Hematology Departement, Centre Hospitalier, Versailles, France
- ²⁹ Hematology Departement, Centre Hospitalier Universitaire, Caen, France
- ³⁰ Hematology Departement, Hopital Pitie Salpetriere, APHP and Paris 6 University Paris, France
- ³¹ Hematology Departement, Centre Hospitalier Universitaire, Rennes, France
- ³² Oncology Departement, Centre Rene Huguenin, Saint Cloud, France
- ³³ Hematology Departement, Hopital Saint Antoine, APHP, and Paris 6 University Paris, France
- ³⁴ Hematology Departement, Centre Hospitalier Universitaire, Tours, France
- ³⁵ Departement de Recherche Clinique, Hopital Saint Louis, APHP, France

³⁶Biology Departement, Centre Hospitalier Universitaire, Lille, France

³⁷Hematology Departement, Service Hematologie Seniors, Hopital Saint Louis, APHP, and Paris 7 University Paris, France

³⁸Hematology Departement, Hopital Cochin, APHP, and Paris 5 University Paris, France

Corresponding author:

Pierre FENAUX, MD, PhD

Service d'hematologie seniors

Hopital Saint Louis

1 avenue Claude Vellefaux, 75475 Paris, France

E mail : pierre.fenaux@aphp.fr

Key words : myelodysplasia, erythropoietin, lenalidomide, low-risk, transfusion

Text word count: 3814

Abstract word count: 199

Figure count : 4

Table count : 5

Reference count: 35

Scientific category: Original Article, Clinical Trial

Disclosures of conflict of interest :

- PF has received honoraria and research funding from Celgene Corporation
- FD has received honoraria from Celgene and Novartis.
- No competing financial interest to declare for the others authors.

ABSTRACT

After failure of erythropoiesis-stimulating agents (ESA), Lenalidomide (LEN) yields red blood cells (RBC) transfusion independence (TI) in 20-30% of lower risk non-del5q MDS. Several observations suggest an additive effect of ESA and LEN in this situation. We performed a randomized phase III study in 131 RBC transfusion-dependent (TD, median transfusion requirement 6 RBC units/8weeks) lower risk ESA-refractory non-del5q MDS. Patients received LEN alone, 10mg/day, 21 days/4 weeks (L arm) or LEN (same schedule) + erythropoietin (EPO) beta, 60,000U/week (LE arm).

In an intent-to-treat (ITT) analysis, erythroid response (HI-E, IWG 2006 criteria) after 4 treatment cycles (primary endpoint) was 23.1% (95% CI: 13.5-35.2) in the L arm and 39.4% (95%CI: 27.6-52.2) in the LE arm ($p=0.044$), while RBC transfusion independence (TI) was reached in 13.8 and 24.2% of the patients in the L and LE arms, respectively ($p=0.13$). Median response duration was 18.1 and 15.1 months in the L and LE arms, respectively ($p=0.47$). Side effects were moderate and similar in the 2 arms. Low baseline serum EPO level and a G polymorphism of *CRBN* gene predicted HI-E.

Combining LEN and EPO significantly improves erythroid response over LEN alone in lower risk non-del5q MDS patients with anemia resistant to ESA.

INTRODUCTION

Myelodysplastic syndromes (MDS) are clonal hematopoietic disorders characterized by ineffective hematopoiesis leading to blood cytopenias and a variable risk of evolution to acute myeloid leukemia (AML)⁽¹⁾.

In International Prognostic Scoring System (IPSS)^{(2),(3)} Low or Intermediate-1 risk patients (“lower risk” MDS), the risk of AML progression is relatively low, survival generally prolonged, and treatment of anemia is the main therapeutic challenge in most cases. In the absence of isolated chromosomal 5q deletion (del5q), erythropoiesis-stimulating agents (ESA) give 30 to 50% erythroid responses, with a median response duration of about 2 years^{(4),(5),(6),(7),(8)}.

Second line treatments after relapse or resistance to ESA include hypomethylating agents, yielding response rates between 25 to 35%⁽⁹⁾, while various other agents are currently being evaluated, including lenalidomide (LEN).

LEN, a thalidomide analogue, yields 60 to 70% erythroid response (HI-E) and transfusion independence (TI) in lower risk MDS patients with del5q^{(10),(11),(12)}, and is approved in this situation in many countries. In lower risk MDS patients without del5q resistant to ESA alone, LEN yields lower TI rates of 20% to 30%^{(10),(13),(14),(15)}. However, our recent clinical experience suggested that the response rate to LEN could be increased by the addition of ESA⁽¹⁴⁾.

To analyze more precisely this finding, we designed a phase III prospective open label randomized trial comparing LEN alone and LEN combined to erythropoietin (EPO) as second

line treatment in non del5q RBC transfusion-dependent lower risk MDS patients with primary or secondary resistance to ESA.

METHODS

Patients

Main inclusion criteria were: (i) MDS according to World Health Organisation (WHO) 2008 criteria⁽¹⁶⁾, with Low or Intermediate-1 IPSS and ECOG status ≤ 2 , (ii) no del5q based on conventional chromosomal or (if less than 20 mitoses were obtained) FISH analysis, (iii) RBC transfusion dependence (TD) ≥ 4 packed RBC units during the 8 weeks before inclusion (administered at hemoglobin levels $< 9\text{g/dl}$), (iv) no erythroid response to epoetin ($\geq 60,000$ Units/week) or darbepoetin ($\geq 250 \mu\text{g/week}$) administered during at least 12 consecutive weeks (i.e. a sufficient treatment duration to assess response according to most studies and recommendations)⁽¹⁷⁾ or relapse after an initial response, both defined according to International Working Group (IWG) 2006 criteria⁽¹⁸⁾, (v) platelet count $> 50\text{G/L}$ and absolute neutrophil count (ANC) $> 0.5\text{G/L}$, and (vi) written informed consent.

Patients receiving chelation therapy were eligible if chelation was continued at similar dosage, but onset of chelation therapy was not allowed during the trial.

The study was approved by an ethics committee (CPP Ile-de-France X) and registered at clinicaltrials.gov ([NCT01718379](https://clinicaltrials.gov/ct2/show/study?term=NCT01718379)), EudraCT number 2008-008262-12.

Study design

This was a two-parallel arms open multicenter phase III clinical trial. Randomization between the two arms (1:1) was centralized and performed at the Unité de Recherche Clinique, Hôpital Cochin (Paris), using computerized lists based on permutation blocks stratified by centers. Patients were randomized between the LEN (L) arm: LEN alone 10 mg/day for 21 days every

28 days, and the LEN plus EPO (LE) arm: same LEN schedule combined to epoetin beta (60,000 units/week) (Figure 1). Celgene (Summit, NJ, USA) and Roche (Basel, Switzerland) provided Lenalidomide and epoetin beta, respectively, for the study, along with a research grant, but were not involved in data analysis and reporting.

Blood counts were monitored weekly during the first four months of treatment, and every two weeks thereafter. The LEN dose was reduced to 5mg/day if ANC decreased below 1G/L and/or platelets below 50G/L, with further dose reductions to 5mg every other day and 5mg twice a week. The use of G-CSF was not allowed in case of neutropenia, due to its potential effect on the erythroid lineage when combined to an ESA⁽⁵⁾.

Responders after 4 cycles were planned to continue the same treatment until relapse. A new bone marrow aspirate and cytogenetic analysis were performed after 4 cycles, and then every 6 months in responders.

Assessment of response and safety

The primary endpoint chosen for the trial was HI-E according to IWG 2006 criteria⁽¹⁸⁾ after 4 treatment cycles, *i.e.* reduction of RBC transfusions of at least 4 units during the 8 weeks prior to evaluation compared to the pretreatment period, for transfusions performed at hemoglobin levels <9g/dL.

Secondary endpoints were TI, defined by the absence of RBC transfusion during the 8 weeks before evaluation, HI-E duration, time to progression to higher risk MDS or AML, and treatment safety. Adverse events were assessed using NCI-CTC version 3.0.

All responses were blindly reviewed by an independent committee (composed of Dr V. Santini, Firenze, Italy, and Dr A. Giagounidis, Dusseldorf, Germany).

CRBN polymorphism

Genetic studies were performed on marrow genomic DNA collected at inclusion. *Cereblon* (*CRBN*) gene A>G polymorphism located in the 5'UTR was analyzed, as previously described⁽¹⁹⁾.

Sample size justification

Sample size computation was based on the primary endpoint, assuming a response rate of 30% and 57% in the control and experimental arms, respectively, based on previous findings with LEN alone and LEN combined to an ESA^{(13),(14)}. With a type I and type II error rates fixed at 0.05 and 0.20, respectively, a minimum of 63 patients had to be enrolled in each randomized arm, based on a two-sided chi-square test with continuity correction.

Statistical analysis

Summary statistics were reported as median [interquartile range, IQR] for continuous variables and percentages otherwise. Analysis was based on the intent-to-treat (ITT) principle, including all patients allocated to their randomized arm whatever the treatment actually administered, except in case of consent withdrawal. All patients without response evaluation at 4 courses (primary endpoint) were considered as failures; such a simple imputation was used in all the manuscript unless specified in the text. Reasons for patient discontinuation that could be informative about treatment effectiveness were tabulated. Sensitivity analyses to such an assumption were then performed, assuming failure in one arm and response in the other arm. The response rate was estimated with 95% confidence interval (95%CI), compared between the randomized arms by the Chi-square test. Multivariate logistic regression was then performed to assess the prognostic set of baseline characteristics of the patients. Treatment-by-covariates interactions were tested using the Gail and Simon statistics⁽²⁰⁾. Time to failure data (response duration) were analyzed using Kaplan-Meier estimate and log-rank test.

All statistical tests were two-sided, with p-values of 0.05 or less denoting statistical significance. All analyses were performed on SAS 9.3 (SAS Inc, Cary, NC) and R version 3.0.2 (2013-09-05) (<http://www.R-project.org/>) packages.

RESULTS

Baseline patient characteristics

132 patients from 34 French centers were included from July 2010 to June 2012, 66 patients *per* treatment arm. One patient withdrew consent before the onset of treatment, and the ITT analysis was therefore performed in the 131 remaining patients. Baseline characteristics of the two arms are summarized in **Table 1**.

Median age at inclusion was 73 years [IQR: 64-77] and M/F ratio was 2. According to WHO classification, there were 57 (43.5%) refractory anemia with ring sideroblasts (RARS), 24 (18.3%) refractory cytopenia with multilineage dysplasia and ring sideroblasts (RCMD-RS), 22 (16.7%) refractory anemia with excess blasts type 1 (RAEB1), 15 (11.5%) refractory cytopenia with multilineage dysplasia (RCMD), and 13 (9.9%) unclassified MDS (MDS-U).

According to classical IPSS, 57 (43.5%) and 74 (56.5%) patients had Low and Intermediate-1 risk, respectively. The median number of RBC units administered during the 8 weeks before inclusion in this series was quite high, i.e. 6 units [IQR 4-8]. Most (n=110, 84.0%) patients had favorable cytogenetics according to classical IPSS, while no patient had unfavorable cytogenetics. Median serum EPO level was 225.5 U/l [IQR: 69-498.5]. Eighty-one (61.8%) of the patients had primary resistance to ESA, and 50 (38.1%) had relapsed after an erythroid response (Table 1).

Twenty-one patients (16.0%), 11 in the L arm and 10 in the LE arm, were also refractory to azacitidine administered after ESA failure, and were included after a wash-out period of at

least 3 months. At inclusion, 62 (47.3%) patients were receiving iron chelation with deferasirox.

Treatment courses and observed responses

A total of 32 patients did not receive the 4 planned courses, 16 in each randomized arm, due to adverse events (n=21), early death (n=4), investigator's or patient's decision (n=5), suicide (n=1), loss-to follow-up (n=1). One patient (LE arm) did not receive any treatment because of early death, 10 patients received only one course (5 in each randomized arm), 10 patients received two courses (3 in the L arm and 7 in the LE arm) and 11 patients received three courses (8 in the L arm and 3 in the LE arm) (Figure 2).

Among the 99 (75.6%) patients who received at least 4 cycles of treatment, 49 patients in the L arm and 50 patients in the LE arm, HI-E after 4 cycles was observed in 15 (30.6%) patients in the L arm and 26 (52%) patients in the LE arm, while TI was achieved in 25 patients, including 9 (18.3%) and 16 (32%) in the L and LE arm, respectively.

ITT analyses

Based on the ITT analysis, HI-E after 4 cycles was 23.1% (15/65) in the L arm (95%CI: 13.5-35.2) and 39.4% (26/66) in the LE arm (95%CI: 27.6-52.2; p=0.044 by the Chi-square test). Sensitivity analyses mostly reached similar conclusions (**Table 2**). TI was achieved in 13.8% (9/65) and 24.2% (16/66) of the patients in the L and LE arms, respectively (p=0.13 by the Chi-square test). The median time to erythroid response was estimated at 4 months in both arms. In patients who achieved transfusion independence, the mean peak increase in hemoglobin level compared to baseline was 1.8 g/dL (range 0.5-2.5) and 2.6 g/dL (range 0.5-8.2) in the arm L and LE, respectively, with no significant difference between the two arms.

Seven (33%) of the 21 patients with baseline cytogenetic abnormalities achieved HI-E after 4 cycles, but none of them achieved cytogenetic response.

Among the 58 non-responders after the 4th cycle, who therefore discontinued treatment, late responses were observed in 2 patients (one in each arm), 4 and 6 weeks after evaluation in the L and LE arm, respectively. However, they were not included as responders for subsequent analyses.

Relapse after erythroid response occurred in 7 of the 15 responders in the L arm and in 13 of the 26 responders in the LE arm. Median response duration was estimated at 18.1 months (95%CI: 7.6-NA) in the L arm, and 15.1 months (95%CI: 10.5-NA) in the LE arm ($p=0.64$ by the log-rank test) (**Figure 3**). Fourteen patients (7 in each arm) were still responders at the end of the study (*i.e.* at 2 years), 12 of them (5 in L arm and 7 in LE arm) being TI. Median TI duration was 18.5 months (95%CI: 12.69-NA) in the L arm, and 11 months (95%CI: 6.07-NA) in the LE arm ($p=0.31$ by the log-rank test).

Prognostic factors of response

None of the following pretreatment factors: gender, age, WHO classification, cytogenetics (according to classical IPSS), classical IPSS, type of ESA resistance (primary or secondary) had any significant impact on HI-E in the two treatment arms (**Table 3**). By contrast, baseline serum EPO level below 100 UI/l (OR= 3.3, 95%CI: 1.35-7.9; $p=0.0087$) and presence of the G allele at *CRBN* rs1672753 (OR= 2.6, 95%CI: 1.09-6.3; $p=0.032$) were associated with a better response rate (**Table 3**). When considered jointly with the randomization arm into a multivariate logistic model based on the 99 patients who were tested for *CRBN* rs1672753 polymorphism, both the treatment arm (OR= 5.0, 95%CI: 1.64-15.1; $p=0.0047$) and baseline serum EPO level (OR= 4.05, 95%CI: 1.3-12.6; $p= 0.016$) were found to add predictive information to each other (Table 4).

We then searched for treatment-by-covariates interaction to assess whether the difference in HI-E response rate after 4 cycles between the 2 randomized arms depended on baseline patient characteristics. No evidence of any difference in the benefit of LE was found according to those characteristics except for RBC transfusion requirement, where the benefit of LE was restricted to patients who had received, over the 8 weeks prior to inclusion, 4 RBC units (OR= 6.6, 95%CI: 2.08-21.4) compared to those who had received >4 RBC units (OR=1.32, 95%CI: 0.87-2.01) ($p=0.010$ by the Gail and Simon test) (**Figure 4**). Thus, in the 39 patients who had received only 4 RBC units in the 8 weeks before inclusion (18 patients in L arm and 21 patients in LE arm), the TI rate was significantly higher in the LE arm (10/21 patients, 47.6%) than in the L arm (3/16 patients, 18.7%) ($p=0.04$).

Of note also that for karyotype, the benefit of LE appeared to be restricted to patients with favorable cytogenetics (representing 84% of the patients), with borderline significance ($P=0.056$ by the Gail and Simon test) (Figure 4).

Finally, in the 50 patients with serum EPO levels ≥ 100 U/L there were 5/24 (21%) erythroid responses in the L arm and 10/26 (38%) in the LE arm ($p=0.10$).

Toxicity

Hematological and non hematological toxicity was comparable in the two treatment arms. Before the end of the fourth cycle, grade 3 and 4 non hematological adverse events (AEs) were observed in 25% of the patients, including deep vein thrombosis (DVT) in 4 patients (3 in the L arm and 1 in the LE arm) (**Table 4**), while grade 3 or 4 myelosuppression occurred in 25% of the cases and included neutropenia in 21% and 18% of patients in the L and LE arm, respectively, and thrombocytopenia in 3% and 7% of patients, respectively, with no difference between the two arms (**Table 5**).

During the first 4 cycles, the dose of LEN was reduced in 31% and 36% of the patients in the L and LE arm, respectively, and the mean daily dose of LEN administered was 8.4 mg in both arms. After the 4th cycle, LEN doses had to be reduced in 50% and 57% of responders in the L and LE arm respectively, and the mean daily doses of LEN administered were 8.5 mg in arm L and 8.1 mg in arm LE.

DISCUSSION

In this randomized study, LEN combined with EPO induced a significantly higher erythroid response rate than LEN alone in ESA-resistant RBC TD lower risk MDS without del5q. The estimated HI-E response rate among all the population was 39.4% in the LE arm compared to 23.1% in the L arm, and these figures reached 52% and 30.6%, respectively, in patients who received at least 4 cycles of treatment. However, RBC-TI rates were not significantly different between the 2 treatment arms (24.2% in the L arm *versus* 13.8 % in the LE arm, $p=0.13$).

All patients included in the study could be considered resistant to ESA, combined or not to G-CSF or were in relapse after an initial response. Indeed, although some responses to ESA (+/- G-CSF) may occur after more than 12 weeks, this is relatively rare, and most treatment guidelines use a 12 weeks period of treatment with at least 60,000 units of EPO or 250 µg of darbepoetin per week to define ESA resistance^{(6),(21)}.

The rationale for combining an ESA to LEN treatment was based on the hypothesis that LEN could restore sensitivity of MDS erythroid progenitors to EPO. Biological studies have demonstrated that LEN increases the expansion of normal mature erythroid progenitors of CFU-E type in the presence of EPO⁽²²⁾. The Cereblon protein, encoded by the *CRBN* gene, is the molecular target of LEN and a substrate receptor of CRBN-CRL4 E3 ubiquitin ligase complex. Recent evidence shows that LEN binding to Cereblon induces the proteosomal

degradation of casein kinase 1A, a protein encoded by CSNK1A1 located in 5q33.1 in myeloid cells with a del5q, while Cereblon targets in non del5q MDS remain to be determined⁽²³⁾. Thus, the mechanism of action of LEN is still unclear in these cells. However, LEN may directly improve EPO receptor signaling in non del5q cells by inhibiting the protein tyrosine phosphatase CD45, leading to the reversal of CD45-induced inhibition of EPO-R/STAT5 signaling, and also by improving the membrane lipid raft integrity, and thus the EPO receptor platform^{(24),(25)}. A clinical benefit of LEN combined to ESA in lower risk MDS without del5q resistant to ESA alone had been observed in a French non randomized compassionate program, where 36% and 55% of the patients who received LEN alone and LEN combined with an ESA, respectively, achieved HI-E⁽¹⁴⁾. In another report from Moffitt's center⁽²⁶⁾, 4 of 19 (21%) lower risk MDS patients resistant to an ESA alone and to LEN alone responded to a LEN+ESA combination.

Our response rate in the L arm was apparently somewhat lower than that obtained by Raza et al.⁽¹³⁾ in a similar population (where RBC TI was achieved in 26% of the cases, compared to 13.9% in our hands). However, in Raza et al's study⁽¹³⁾, ESA resistance was not documented in all patients (contrary to the present study). In that study⁽¹³⁾, patients who fulfilled our inclusion criteria (at least 4 RBC concentrates administered for Hb<9g/dL in the 8 weeks preceding study treatment) had a TI rate of 17%, similar to our results in the L arm. In another recent study using LEN alone (MDS 005 study)⁽¹⁵⁾ in a similar population, so far presented only in abstract form, RBC-TI was achieved in 26.7% of the patients. There was no RBC minimal transfusion requirement in Raza et al. study⁽¹³⁾ and a minimal transfusion requirement of 1.5 RBC units/28 days in MDS-005 study⁽¹⁵⁾, compared to 4 units/8 weeks in the present study, possibly explaining the higher transfusion burden we observed.

In previous studies of lower risk MDS patients without del5q treated with LEN^{(13),(14),(26)}, TD<2 units/month, platelets>150G/L, shorter duration of MDS, lower LDH level, favorable

karyotype⁽¹³⁾, lower serum EPO level⁽²⁶⁾, and more favorable WHO classification⁽¹⁴⁾ were associated with higher HI-E. In our study, baseline EPO level was the only conventional factor predicting HI-E, and it was the only prognostic factor in multivariate analysis. We also confirmed the predictive value for HI-E of a G polymorphism in the 5' UTR of the *CRBN* gene⁽¹⁹⁾ in univariate analysis. The predictive value of this G polymorphism should however be confirmed in an external cohort. In addition, reasons for this possible impact of *CRBN* rs1672753 on response to LEN, with or without EPO, in MDS cells remain to be identified. We also found that only patients with favorable karyotype according to conventional IPSS seemed to benefit from the addition of EPO to LEN. However, this cytogenetic category represented 84% of the patients included. The absence of cytogenetic responses after 4 months in patients with baseline cytogenetic abnormalities in our study may support a different mechanism of action of the drug in MDS without del5q and MDS with del5q where LEN often leads to cytogenetic response⁽²⁷⁾.

Response duration and TI duration did not significantly differ between the 2 arms (median duration of 18.1 versus 14.6 months, and 18.5 and 11 months in the L and LE arm, respectively). By comparison, median TI duration with LEN alone was 10 months in Raza et al.'s study⁽¹³⁾, 8.2 months in Santini et al.'s study⁽¹⁵⁾.

Side effects were similar in the 2 arms. Severe neutropenia and thrombocytopenia with LEN are less frequent and less profound in non del5q than in del5q patients. In Raza et al.'s study⁽¹³⁾, the incidence of grade 3 or 4 neutropenia and thrombocytopenia was 25% and 20% respectively, with little difference observed between patients receiving the 10 mg daily and 21-day lenalidomide schedule. The incidence of grades 3 or 4 neutropenia and thrombocytopenia was similar in our study, 24% and 25% respectively, and those cytopenias were the major reasons for early treatment discontinuation. Still, about 20% of the patients had early protocol discontinuation due to side effects, mainly cytopenias, and the dose of

LEN had to be reduced in 31% and 36% of the patients in the L and LE arm, respectively, also due to cytopenias. These results suggest that a daily dose of LEN of 10mg during 3 weeks every 4 weeks may be too high in a substantial proportion of the patients. A lower starting dose may have to be considered in future studies, in order to avoid early discontinuation by many patients. Management recommendations, based to some extent on those published for LEN in lower risk MDS with del 5q⁽²⁸⁾ could also be useful. In MDS 005 study⁽²⁷⁾, grade 3-4 neutropenia and thrombocytopenia were reported in 62% and 36% of the patients, respectively.

In our study, non hematological grade 3 and 4 toxicity was rare and included DVT in 3% of patients. Of note, the addition of high dose EPO did not increase the incidence of thrombotic events.

Our current results with LEN and EPO appear at least equivalent to those reported in lower risk MDS without del5q resistant to ESA treated with hypomethylating agents, in our experience⁽²⁹⁾ and in a Nordic study⁽³⁰⁾. Interestingly, we found in lower risk MDS without del5q resistant to ESA that the addition of EPO did not improve the response rate to AZA⁽²⁹⁾ (manuscript in preparation). Other treatments in this situation have yielded only modest results. Immunosuppressive treatment with anti-thymocyte globulin with or without cyclosporine or with alemtuzumab can yield response rates i.e. TI up to 30 to 40%, but in highly selected patient populations^{(31),(32)}. Among innovative agents, the glutathione-S-transferase P1-1 (GSTP1-1) inhibitor Ezatiostat and the MAP kinase inhibitor ARRY 614 both gave a 29% erythroid response rate in heavily pretreated lower risk MDS without del5q^{(33),(34)}, while early results using drugs with TGF beta pathway ligand traps (ACE 011 and ACE 536) appear promising^{(15),(35)}.

A possible weakness of our work is that we chose HI-E according to IWG 2006 criteria, but not RBC-TI, as primary study endpoint, and that the patient number was not powered on the RBC-TI endpoint. Achieving TI, and not only a significant reduction of transfusion requirement, may indeed be considered as a better endpoint from a clinical perspective, and most recent clinical studies in lower risk MDS have chosen TI as primary endpoint, an endpoint that may also be required by health agencies like FDA and EMA ^{(13),(27)}. There was indeed no significant difference in TI rates in the whole patient series between the L and the LE arm. However, in this very heavily transfusion dependent population, when we restricted the analysis to patients who had received only 4 RBC units/8weeks before inclusion, TI rates were significantly higher in the LE arm than in the L arm (47% versus 16%, $p=0.04$).

In conclusion, our prospective phase III randomized study shows that a LEN plus EPO combination can yield higher erythroid response rates than LEN alone in lower risk MDS without del 5q resistant to ESA. This did not translate into a significant improvement of RBC-TI rate, possibly due to the insufficient size of our patient population or to the high transfusion burden in our patients, as TI rate differences were significant between the 2 treatment arms when the analysis was restricted to patients who did not receive more than 4 RBC units in the 8 weeks before inclusion. Tolerance of this treatment association was generally acceptable, although combinations using a lower initial dose of LEN may have to be explored to avoid early treatment discontinuation in a substantial proportion of the patients.

ACKNOWLEDGEMENTS

The authors thank Fatiha Chermat and Rosa Sapena from the Groupe Francophone des Myelodysplasies (GFM) for the management, logistical and administrative assistance.

Research was supported by Celgene (Summit, NJ) and Roche (Basel, Switzerland) who provided Lenalidomide and epoetin beta, respectively, along with a research grant.

AUTHORSHIP CONTRIBUTIONS

AT performed clinical research, analyzed data, and wrote the paper

OK performed biological research, and wrote the paper

SC analyzed data and wrote the paper

AR, JD, AS, CR, OBR, AB, AGB, SW, DC, KL, BDR, DB, CG, BS, LS, VS, RP, BG, PCM, BC, CS, RB, LL, EW, GT, KB, FG, ALT, SC, KM, SN, CS, FI, EG, CP : performed research, and wrote the paper

MF, PF, FD: designed research, analyzed data, and wrote the paper

DISCLOSURES OF CONFLICTS OF INTEREST

PF has received honoraria and research funding from Celgene Corporation.

FD has received honoraria from Celgene and Novartis.

No competing financial interest are to declare for the others authors.

REFERENCES

1. Ades L, Itzykson R, Fenaux P. Myelodysplastic syndromes. *Lancet*. 2014;383(9936):2239-52.
2. Greenberg P, Cox C, LeBeau MM, Fenaux P, Morel P, Sanz G, et al. International scoring system for evaluating prognosis in myelodysplastic syndromes. *Blood*. 1997;89(6):2079-88.
3. Greenberg PL, Tuechler H, Schanz J, Sanz G, Garcia-Manero G, Sole F, et al. Revised international prognostic scoring system for myelodysplastic syndromes. *Blood*. 120(12):2454-65.
4. Hellstrom-Lindberg E, Ahlgren T, Beguin Y, Carlsson M, Carneskog J, Dahl IM, et al. Treatment of anemia in myelodysplastic syndromes with granulocyte colony-stimulating factor plus erythropoietin: results from a randomized phase II study and long-term follow-up of 71 patients. *Blood*. 1998;92(1):68-75.
5. Casadevall N, Durieux P, Dubois S, Hemery F, Lepage E, Quarre MC, et al. Health, economic, and quality-of-life effects of erythropoietin and granulocyte colony-stimulating factor for the treatment of myelodysplastic syndromes: a randomized, controlled trial. *Blood*. 2004;104(2):321-7.
6. Park S, Grabar S, Kelaidi C, Beyne-Rauzy O, Picard F, Bardet V, et al. Predictive factors of response and survival in myelodysplastic syndrome treated with erythropoietin and G-CSF: the GFM experience. *Blood*. 2008;111(2):574-82.
7. Jadersten M, Malcovati L, Dybedal I, Della Porta MG, Invernizzi R, Montgomery SM, et al. Erythropoietin and granulocyte-colony stimulating factor treatment associated with improved survival in myelodysplastic syndrome. *J Clin Oncol*. 2008;26(21):3607-13.
8. Greenberg PL, Sun Z, Miller KB, Bennett JM, Tallman MS, Dewald G, et al. Treatment of myelodysplastic syndrome patients with erythropoietin with or without granulocyte colony-stimulating factor: results of a prospective randomized phase 3 trial by the Eastern Cooperative Oncology Group (E1996). *Blood*. 2009;114(12):2393-400.
9. Sekeres MA, Steensma DP. Defining prior therapy in myelodysplastic syndromes and criteria for relapsed and refractory disease: implications for clinical trial design and enrollment. *Blood*. 2009;114(13):2575-80.
10. Corral LG, Haslett PA, Muller GW, Chen R, Wong LM, Ocampo CJ, et al. Differential cytokine modulation and T cell activation by two distinct classes of thalidomide analogues that are potent inhibitors of TNF-alpha. *J Immunol*. 1999;163(1):380-6.
11. List A, Kurtin S, Roe DJ, Buresh A, Mahadevan D, Fuchs D, et al. Efficacy of lenalidomide in myelodysplastic syndromes. *N Engl J Med*. 2005;352(6):549-57.
12. List A, Dewald G, Bennett J, Giagounidis A, Raza A, Feldman E, et al. Lenalidomide in the myelodysplastic syndrome with chromosome 5q deletion. *N Engl J Med*. 2006;355(14):1456-65.
13. Raza A, Reeves JA, Feldman EJ, Dewald GW, Bennett JM, Deeg HJ, et al. Phase 2 study of lenalidomide in transfusion-dependent, low-risk, and intermediate-1 risk myelodysplastic syndromes with karyotypes other than deletion 5q. *Blood*. 2008;111(1):86-93.
14. Sibon D, Cannas G, Baracco F, Prebet T, Vey N, Banos A, et al. Lenalidomide in lower-risk myelodysplastic syndromes with karyotypes other than deletion 5q and refractory to erythropoiesis-stimulating agents. *Br J Haematol*. 156(5):619-25.
15. Komrokji R G-MG, Ades L, Laadem A, Vo B, Prebet T, et al. . An Open-Label, Phase 2, Dose-Finding Study of Sotatercept (ACE-011) in Patients with Low or Intermediate-1 (Int-1)-Risk Myelodysplastic Syndromes (MDS) or Non-Proliferative Chronic Myelomonocytic Leukemia (CMML) and Anemia Requiring Transfusion. *ASH Annual Meeting Abstracts*. 2014;abstract 3251.
16. Vardiman JW, Thiele J, Arber DA, Brunning RD, Borowitz MJ, Porwit A, et al. The 2008 revision of the World Health Organization (WHO) classification of myeloid neoplasms and acute leukemia: rationale and important changes. *Blood*. 2009;114(5):937-51.
17. Malcovati L, Hellstrom-Lindberg E, Bowen D, Ades L, Cermak J, Del Canizo C, et al. Diagnosis and treatment of primary myelodysplastic syndromes in adults: recommendations from the European LeukemiaNet. *Blood*. 2013;122(17):2943-64.

18. Cheson BD, Greenberg PL, Bennett JM, Lowenberg B, Wijermans PW, Nimer SD, et al. Clinical application and proposal for modification of the International Working Group (IWG) response criteria in myelodysplasia. *Blood*. 2006;108(2):419-25.
19. Sardnal V, Rouquette A, Kaltenbach S, Bally C, Chesnais V, Leschi C, et al. A G polymorphism in the CRBN gene acts as a biomarker of response to treatment with lenalidomide in low/int-1 risk MDS without del(5q). *Leukemia*. 27(7):1610-3.
20. Gail M, Simon R. Testing for qualitative interactions between treatment effects and patient subsets. *Biometrics*. 1985;41(2):361-72.
21. Fenaux P, Haase D, Sanz GF, Santini V, Buske C, Group EGW. Myelodysplastic syndromes: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Annals of oncology : official journal of the European Society for Medical Oncology / ESMO*. 2014;25 Suppl 3:iii57-69.
22. Narla A, Dutt S, McAuley JR, Al-Shahrour F, Hurst S, McConkey M, et al. Dexamethasone and lenalidomide have distinct functional effects on erythropoiesis. *Blood*. 118(8):2296-304.
23. Fink E, Krönke J, Slater NH et al. Lenalidomide Induces Ubiquitination and Degradation of CSNK1A1 in MDS with Del(5q). *ASH Annual Meeting Abstracts*. 2014;124(abstract 4).
24. List A EM, Gao G, et al. Large CD45 Protein Tyrosine Phosphatase (PTP) Isoforms Predominate in Myelodysplastic Erythroid Precursors and Attenuate the Erythropoietin (EPO): STAT5 Signal. *ASH Annual Meeting Abstracts*. 2006;108(abstract 2650).
25. McGraw KL BA, Johnson J, et al. Lenalidomide Induces Lipid Raft Assembly to Enhance Erythropoietin Receptor Signaling in Myelodysplastic Syndrome Progenitors. *ASH Annual Meeting Abstracts*. 2014;124(abstract 4623).
26. Komrokji RS, Lancet JE, Swern AS, Chen N, Paleveda J, Lush R, et al. Combined treatment with lenalidomide and epoetin alfa in lower-risk patients with myelodysplastic syndrome. *Blood*. 120(17):3419-24.
27. Wei S, Chen X, Rocha K, Epling-Burnette PK, Djeu JY, Liu Q, et al. A critical role for phosphatase haploinsufficiency in the selective suppression of deletion 5q MDS by lenalidomide. *Proc Natl Acad Sci U S A*. 2009;106(31):12974-9.
28. Giagounidis A, Fenaux P, Mufti GJ, Muus P, Platzbecker U, Sanz G, et al. Practical recommendations on the use of lenalidomide in the management of myelodysplastic syndromes. *Annals of hematology*. 2008;87(5):345-52.
29. Thepot S BAR, Chevret S, et al. Prognostic Factors Of Response and Survival To Azacitidine (AZA) +/- EPO In RBC Transfusion Dependent (TD) IPSS Low and Int-1 (LR) MDS Resistant To EPO, With Particular Emphasis Of Genetic Lesions: A Study By The GFM. *ASH Annual Meeting Abstracts*. 2013(abstract 658).
30. Tobiasson M, Dybedahl I, Holm MS, Karimi M, Brandefors L, Garelius H, et al. Limited clinical efficacy of azacitidine in transfusion-dependent, growth factor-resistant, low- and Int-1-risk MDS: Results from the nordic NMDSG08A phase II trial. *Blood Cancer J*. 4:e189.
31. Sloan EM, Wu CO, Greenberg P, Young N, Barrett J. Factors affecting response and survival in patients with myelodysplasia treated with immunosuppressive therapy. *J Clin Oncol*. 2008;26(15):2505-11.
32. Sloan EM, Olnes MJ, Shenoy A, Weinstein B, Boss C, Loeliger K, et al. Alemtuzumab treatment of intermediate-1 myelodysplasia patients is associated with sustained improvement in blood counts and cytogenetic remissions. *J Clin Oncol*. 28(35):5166-73.
33. Raza A, Galili N, Smith SE, Godwin J, Boccia RV, Myint H, et al. A phase 2 randomized multicenter study of 2 extended dosing schedules of oral ezatiostat in low to intermediate-1 risk myelodysplastic syndrome. *Cancer*. 118(8):2138-47.
34. Garcia-Manero G, Khoury HJ, Jabbour E, Lancet J, Winski SL, Cable L, et al. A phase I study of oral ARRY-614, a p38 MAPK/Tie2 dual inhibitor, in patients with low or intermediate-1 risk myelodysplastic syndromes. *Clinical cancer research : an official journal of the American Association for Cancer Research*. 2015;21(5):985-94.
35. Platzbecker U GU, Giagounidis A, Goetze K, Kiewe P, Mayer K, et al. ACE-536 Increases Hemoglobin and Reduces Transfusion Burden in Patients with Low or Intermediate-1 Risk

Myelodysplastic Syndromes (MDS): Preliminary Results from a Phase 2 Study. 2014;ASH Annual Meeting Abstracts(abstract 411).

Accepted manuscript

FIGURE LEGENDS**Figure 1 : GFM-LENEPO 2008 study****Treatment plan**

(registered at clinicaltrials.gov ([NCT01718379](https://clinicaltrials.gov/ct2/show/study/NCT01718379)), EudraCT number 2008-008262-12)

Figure 2 : CONSORT 2010 flow diagram of the GFM-LENEPO 2008 study**Figure 3: Response duration according to the randomization arm**

Reported figures are the number of exposed patients in each randomized arm over time

L, Lenalidomide ; LE, Lenalidomide + Erythropoietin.

Figure 4: Search for treatment-by-subset interactions

This forest plot displays the estimated effect of randomized arm on response rate (LE vs L) in patient subsets, using the odds ratio (OR) as the measure of effect. The heterogeneity in OR across the subsets are tested by the Gail and Simon test.

Table 1: Baseline Patient Characteristics overall and according to the randomization arm

Patient characteristics	Randomized Treatment arms		All (n=131)
	L arm (n=65)	LE arm (n=66)	
Age, median (IQR)	73 [64-77]	73.5 [68-76]	73 [64-76]
M/F	1.6	2.6	2
WHO classification, N (%)			
RARS	25 (39.7)	32 (48.5)	57 (43.5)
RCMD-RS	16 (25.4)	8 (12.1)	24 (18.3)
RAEB1	7 (11.1)	15 (22.7)	22 (16.7)
RCMD	6 (9.2)	9 (13.6)	15 (11.5)
MDS-U	11 (16.9)	2 (3.0)	13 (9.9)
Cytogenetics (IPSS), N (%)			
Favorable	56 (86.1)	54 (81.8)	110 (84)
Intermediate	9 (14.1)	12 (18.8)	21 (16)
IPSS, N (%)			
Low	30 (46.1)	27 (40.9)	57 (43.5)
Intermediate-1	35 (54.7)	39 (60)	74 (56.5)
Type of EPO resistance, N (%)			
Primary resistance	39 (60)	42 (63.6)	81 (61.8)

Relapse	26 (40)	24 (36.4)	50 (38.1)
Serum EPO level, U/L median [IQR]	134 [69-306]	185 [72.5-498.5]	225.5 [69-498.5]
Number of RBC units transfused/8wk, median [IQR]	6 [4-8]	6 [4-8]	6 [4-8]
Genetic characteristics	L arm (n=52)	LE arm (n=47)	All (n=99)
<i>CRBN</i> rs1672753 polymorphism, N (%)			
A/A	35 (67.3)	34 (72.3)	69 (69.7)
G/A or G/G	17 (32.7)	13 (27.6)	30 (30.3)

IQR, interquartile range; M/F, male/female; WHO, world health organisation; RARS, refractory anemia with ring sideroblasts; RCMD-RS, refractory cytopenia with multilineage dysplasia; RS, ring sideroblasts; RAEB, refractory anemia with excess blasts; MDS-U, MDS unclassified; IPSS, international prognostic scoring system; EPO, erythropoietin; RBC, red blood cells; *CRBN*, cereblon gene.

Toma et al.

Table 2: Erythroid response according to IWG 2006 criteria (primary endpoint), in the two randomized arms

	L Arm (N=65)	LE Arm (N=66)	p value
Intent-to-treat analysis, N (%)			
Assuming missing outcomes as failures : <i>Primary analysis</i>	15 (23.1)	26 (39.4)	0.044
Sensitivity analyses, N (%)			
Assuming missing outcomes as failures in the L arm and responses in the LE arm	15 (23.1)	42 (63.6)	0.0001
Assuming missing outcomes as responses in the L arm and failures in the LE arm	31 (47.7)	26 (39.4)	0.38
Assessed responses, N (%)	49 (75.4)	50 (75.8)	N=99
Reasons for non-observed outcomes*, N (%)	16 (24.6)	16 (24.2)	N=32
Adverse events	12	9	21
Progression/death	1 (death after 2 cycles)	3	4
Investigator's decision	0	2	2
Patient's decision	2	1	3
Suicide	1 (after 2 cycles)	0	1
Loss to follow-up	0	1 (after 2 cycles)	1

*All due to treatment discontinuation before the end of the 4th course;

L, Lenalidomide; LE, Lenalidomide + Erythropoietin.

Table 3: Prognostic factors of erythroid response: univariate analysis

Variable	Number of patients	Number of HI-E response	% HI-E	OR (95%CI)	P-value
Gender					
Female	43	10	23.3	1.00	0.17
Male	88	31	35.3	1.8 (0.78-4.12)	
Age					
<70 years	45	12	26.7	1.00	0.41
≥70 years	86	29	33.7	1.4 (0.63-3.11)	
WHO classification					
RARS	57	17	29.8	1.00	0.41
RCMD-RS	24	5	20.8	0.6 (0.20-1.93)	
RAEB1	22	8	36.4	1.3 (0.48-3.79)	
RCMD	15	8	53.3	2.7 (0.84-8.60)	
MDS-U	13	3	23.1	0.7 (0.17-2.89)	
Cytogenetics (IPSS)					
Intermediate	21	7	33.3	1.00	0.83
Favorable	110	34	30.9	0.89 (0.33-2.42)	
Risk (IPSS)					
Intermediate-1	74	25	33.8	1.00	0.57
Low	55	16	29.1	0.80 (0.38-1.71)	

Type of EPO resistance					
Primary	50	18	36.0	1.00	
Relapse	81	23	28.4	1.42 (0.67-3.01)	0.36
Serum EPO level					
≥100U/L	70	15	21.4	1.00	
< 100U/L	34	16	47.1	3.3 (1.35-7.9)	0.0087
<i>CRBN</i> rs1672753 SNP					
A/A	69	23	38.3	1.00	
G/A or G/G	30	17	56.7	2.6 (1.09-6.3)	0.032

RARS, refractory anemia with ring sideroblasts; RCMD, refractory cytopenia with multilineage dysplasia; RS, ring sideroblasts; RAEB, refractory anemia with excess blasts; MDS-U, MDS unclassified; IPSS, international prognostic scoring system; EPO, erythropoietin; *CRBN*, cereblon gene.

Table 4 : Multivariate analysis

Patients tested for CRBN rs1672753 polymorphism (N=99)	IWG 2006 responses OR (IC95%)	Multivariate analysis p
LE <i>versus</i> L treatment	5.0 [1.64-15.1]	0.0047
M/F	1.79 [0.78 ; 4.12]	NS
IPSS Low <i>versus</i> Intermediate-1	0.80 [0.38 ; 1.71]	NS
Type of EPO resistance : primary <i>versus</i> relapse	1.42 [0.67 ; 3.01]	NS
Serum EPO level < 100 U/L <i>versus</i> ≥ 100 U/L	4.05 [1.3-12.6]	0.016
CRBN A/A <i>versus</i> G/A or G/G	0.38 [0.16 ; 0.92]	0.026

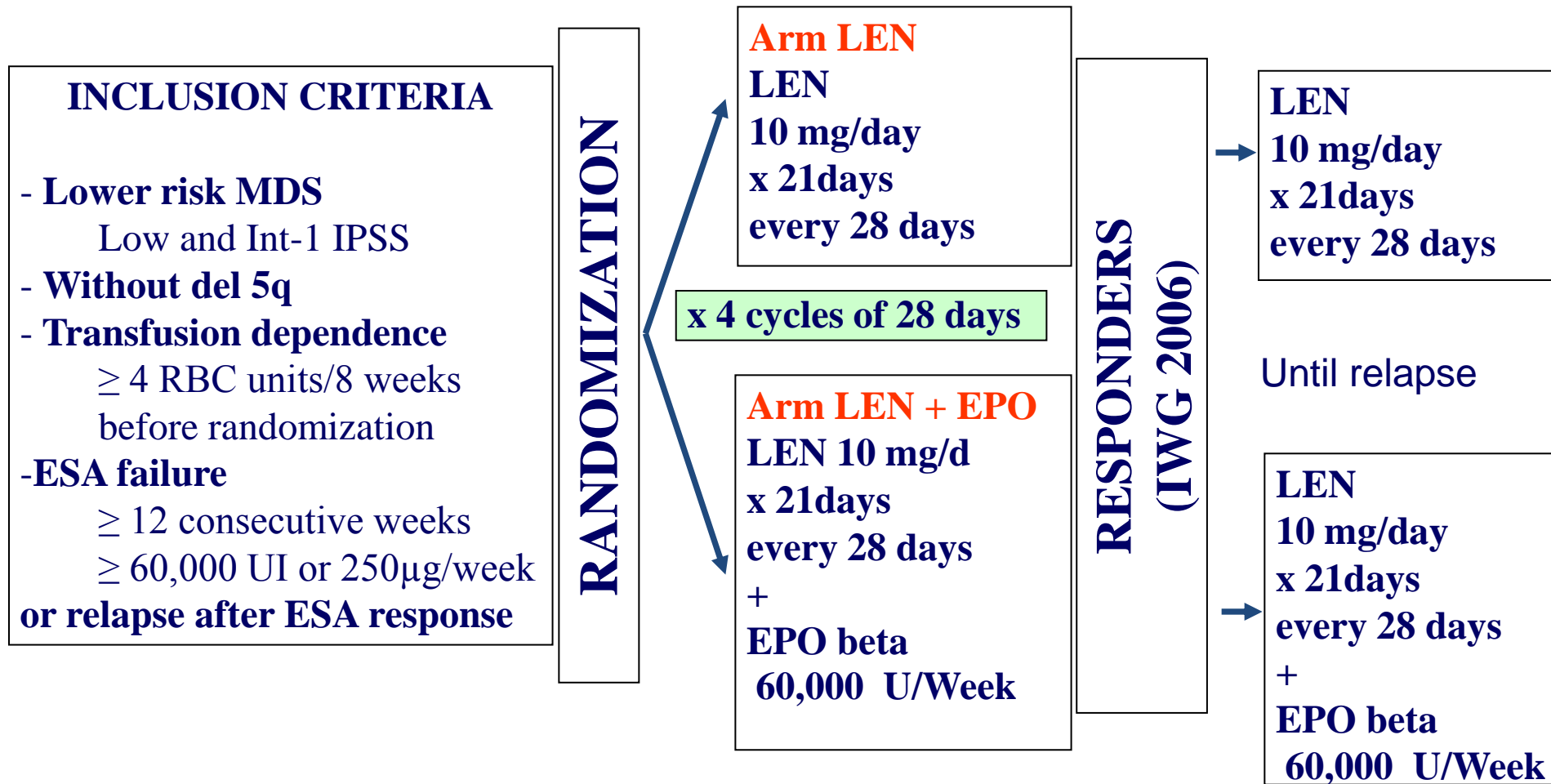
CRBN, cereblon gene ; LE, Lenalidomide + Erythropoietin ; L, Lenalidomide

Table 5 : Grade 3 and 4 adverse events during the first four cycles

Non hematological grade 3-4 AEs before the end of the 4 th cycle (number of patients)	L Arm N=65	LE Arm N= 66
Deep vein thrombosis	3	1
Acute coronary syndrome	1	-
Cardiac failure	3	3
Diarrhea	1	3
Bowel obstruction	2	-
Rash	2	-
Dyspnea	2	2
Pleural effusion	-	1
Renal failure	-	2
Gout	-	2
Other metabolic disorders	-	1
Fatigue	2	3
Hematological grade 3-4 AEs before the end of the 4th cycle (number of patients)		
Neutropenia	14	12
Thrombocytopenia	2	5

AE, adverse event; L, Lenalidomide; LE, Lenalidomide + Erythropoietin.

Toma et al. - Figure 1 : GFM LENEPO 2008 study – Schema and treatment plan



Toma et al. - Figure 2 : CONSORT 2010 Flow diagram

